REMARKS

I. Status of the Priority Document

Applicants respectfully request the Examiner to investigate the status of Applicants' certified copy of their priority document. Applicants submitted a *Request for Acknowledgement of the Priority Document,* along with a copy of the *Notification Concerning Submission or Transmittal of Priority Document*, on November 9, 2001. The PTO replied with a "Response to Request Under PCT Rule 17.2" dated May 17, 2002. That document states: "In accordance with PCT Rule 17.2(a), the [PTO] has requested a copy of application number EP 98203871.3 from the IB. The applicant has no obligation to furnish a certified copy of this priority document to the [PTO]."

The Office Action dated October 7, 2003, however, indicates on the first page that no copy of the certified priority document has been received by the PTO. Since no priority document has been acknowledged, Applicants respectfully request the Examiner to investigate the status of their priority document, and if necessary, ask the International Bureau again to forward a certified copy of the priority document to the PTO so that Applicants can receive the benefits of priority for this application.

II. Status of the Official Filing Receipt

Applicants have not received an Official Filing Receipt for this application. Applicants respectfully request that the Examiner provide Applicants with a copy of the Official Filing Receipt with the next official action.

III. Status f th Claims and Amendments

Claims 1-13 are pending, with claim 1 being independent. Claims 1-11 are amended herein, and claims 12-13 have been added, all without prejudice to pursue canceled subject matter in a continuing application, and without disclaimer of any subject matter. Since the total number of claims does not exceed 20, new claims 12 and 13 do not require additional claims fees.

Claims 1-11 have been amended to conform to U.S. patent claim language conventions, and to correct minor typographical errors. Accordingly, changes to the scope of the claims are not intended. Support for these amendments, therefore, can be found, among other places, in the claims as originally filed.

Claim 1 has been further amended without prejudice to delete those compounds in which R_1 and R_2 form a bridge, and to specifically recite the prodrugs at position R_4. Support for the claimed subject matter can be found throughout the specification and claims as originally filed. Specific support for the claimed prodrugs appears, among other places, in the specification at page 4, lines 5-9.

Claim 10 has also been further amended without prejudice to recite the CNS disorders set forth in the specification at page 3, lines 29-33. The amended claim specifically recites anxiety disorders and also particular anxiety disorders such as panic and obsessive compulsive disorder. This claim should not be rejected because "anxiety disorders" embraces for example, "panic." As provided in the M.P.E.P., such circumstances do not necessarily blur the scope of the claim, and particularly do not do so in this case.

> The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily

> render the scope of the claim unclear. For example, the Markush group, "selected from the group consisting of amino, halogen, nitro, chloro and alkyl" should be acceptable even though "halogen" is generic to "chloro."

M.P.E.P. § 2173.05(h)(I).

New claims 12 and 13 find support, among other places, in the specification at page 1, line 18, to page 2, line 13, and in the examples on pages 5-7.

The specification has been amended to add an abstract on a separate page. Support for this amendment can be found, for example, on the first page of the published PCT application that forms the specification for this application.

IV. Objection Regarding Abstract

The Examiner has objected to the specification, noting the requirement for an abstract in accordance with 37 C.F.R. § 1.72(b). Office Action at 2. Applicants hereby amend the specification by providing an abstract on a separate page. The words of the abstract appear on the front page of the published PCT application, of which this application represents the national stage. Thus, the content of the abstract does not represent the introduction of new matter. The objection should be withdrawn as moot in view of the accompanying abstract.

V. Claim Rejections Under 35 U.S.C. § 112, ¶ 1

A. Rejection Regarding "Bridge" Compounds

Claims 1-11 have been rejected under 35 U.S.C. § 112, ¶ 1 for allegedly lacking enabling disclosure in the specification. Office Action at 2. Specifically, the specification allegedly "does not reasonably provide enablement for preparation and

use of compounds wherein [R1] and R2 form a bridge." *Id.* Applicants do not agree with this rejection.

Without acquiescing to the rejection, Applicants have amended claim 1 to delete those compounds in which R_1 and R_2 form a bridge. Accordingly, this rejection should be withdrawn as moot.

B. Rejection Regarding Claim 10

Claim 10 has been rejected under 35 U.S.C. § 112, ¶ 1 for allegedly lacking enablement. Office Action at 4. While the "claim is interpreted to include any and all [CNS] disorders," allegedly "the specification only discusses the potential use of the compounds in the treatment of anxiety and depression." *Id.* Accordingly, "[c]ompetent evidence of art-recognized efficacy for intended use needs to be provided." *Id.* Applicants respectfully disagree with this rejection.

Without acquiescing to the rejection, Applicants have amended claim 10 to recite the CNS disorders described in the specification on page 3, lines 29-34.

"'The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.'" M.P.E.P. § 2164.01 (quoting *United States v. Teletronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988)). Applicants respectfully contend that their specification, and information known in the pharmaceutical art including information cited in the specification, amply enable the reasonably skilled artisan to make and use the invention of amended claim 10.

The specification and documents cited therein contain ample enabling disclosure, including actual working examples. "Compounds according to the invention show affinities for both the dopamine D_2 receptor (pKi range 7.5-8.5) and the serotonin 5-HT_{1A} receptor (pKi range 7.0-8.0) measured according to well-defined methods[.]" Specification at 2, ll. 15-21 (citations omitted). Partial agonism results and techniques appear at page 2, lines 23-30. Applicants also report broad activities in several animal models on page 2, line 32, to page 3, 27. Specifically, when tested in the rat for anxiolytic/antidepressant activity, "[t]he activity of the compounds in this model was in the low microgram/kg range, which is surprisingly more active (by a factor 100 to 3000) compared to the compounds previously described in EP 0190472 and EP 0398413." *Id.* at 3, ll. 2-5. The compounds of the claimed invention show additional antidepressant effects and dopamine antagonist-like effects at higher doses in other animal models. *Id.* at 3, ll. 7-27. Thus, Applicants have tested and reported actual potencies of their compounds in several *in vitro* and *in vivo* animal models. This testing reveals "value in the treatment of affections or diseases of the central nervous system, caused by disturbances of the dopaminergic and/or serotonergic systems." Specification at 3, ll. 29-31.

The rejection challenges the correlation between the disclosed activity in the several *in vitro* and *in vivo* models, and the claimed therapeutic methods. However, there is no evidence providing any basis to doubt the correlation between the reported activity and the claimed method. "Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example."

M.P.E.P. § 2164.02. Here. no adequate challenge to the correlation appears in the Office Action.

The enablement challenge also amounts to an assertion of incredible utility, requiring a showing equal to that customary before the Food and Drug Administration. "'FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development.'" M.P.E.P. § 2107.01 (quoting *In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995)(internal citation omitted)); *see also* M.P.E.P. § 2164.07 (discussing relationship of enablement requirement to utility requirement of 35 U.S.C. § 101).

Applicants have continued their work with the invention set forth in claim 10, and attach an article reporting their results involving the compound of Example 2. *See* R. Feenstra et al., SLV308, 26(2) Drugs of the Future 128 (2001). In the article, Applicants and their colleagues test the compound of Example 2 according to the protocols cited in the specification. Reference 2 of the article appears in the specification on page 2, lines 17-19, and reference 3 is cited on page 2 of the specification, lines 27-28. *Compare with* Feenstra et al. at 129, col. 2. That such protocols have been used demonstrates the high level of skill in the art. In addition, Applicants and their colleagues report clinical tests on the compound, showing significantly promising results for the pharmacokinetics, metabolism, toxicology, human safety and human tolerability of the compound of Example 2. In sum, "[b]oth the preclinical and clinical data suggest that

SLV308 [compound of Example 2] will be of value in treating parkinsonian patients." Feenstra et al. at 131, col. 2.

Using the teachings of the specification, one of ordinary skill in the art can synthesize the compounds of formula (I) and formulate dosages based on potencies determined according to the disclosed protocols. Synthetic guidance appears in the specification on pages 4-7. Suitable acids for acceptable acid addition salts are given on page 3, line 36, to page 4, line 3. Prodrugs appear on page 4, lines 5-9. Suitable forms for administration can be made by usual processes combining the compound of formula (I) with liquid or solid carrier materials, as discussed on page 4, lines 11-13. That potencies or dosages may vary from compound to compound does not take away from the enablement of the claimed invention. Determining potencies and dosages is routine in the pharmaceutical art, and is amply enabled by Applicants' specification. "[I]t is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation." M.P.E.P. § 2164.01(c).

Applicants respectfully submit that amended claim 10 is amply enabled, and request that this rejection be withdrawn.

C. Rejection Regarding "Prodrug"

Claim 1 has been rejected under 35 U.S.C. § 112, ¶ 1, for allegedly lacking enablement regarding the claim term, "prodrug." Office Action at page 4. Allegedly, "[t]he scope of 'prodrug' is not enabled." *Id.* Applicants respectfully traverse this rejection.

Without acquiescing to the allegation that the scope of the term "prodrug" is not enabled, Applicants have amended claim 1 to recite specific prodrugs at the N-R_4 position. Support for this amendment can be found, among other places, in the specification at page 4, lines 5-9. "Prodrugs are derivatives of the compounds having formula (I) wherein R_4 is a group which is easily removed after administration." *Id.* at ll. 5-6. Applicants then list numerous examples of such groups, which are now recited in claim 1.

Furthermore, one of ordinary skill in the art can practice the claimed invention without undue experimentation. Making the claimed prodrugs can be done following the synthetic guidelines and working examples set forth in the specification, augmented by synthetic techniques known in the art. "A patent need not teach, and preferably omits, what is well known in the art." M.P.E.P. § 2164.01. After forming the claimed prodrugs, the skilled artisan can observe the ease in which the prodrug R_4 group is removed, for example in simulated gastric or other physiologic environments in which pharmaceutical formulations are routinely tested for dissolvability and bioavailability. Such routine tests do not amount to undue experimentation. "The test of enablement is not whether an experimentation is necessary, but whether, if experimentation is necessary, it is undue." M.P.E.P. § 2164.01 (citing *In re Angstat,* 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976)).

Accordingly, Applicants respectfully request that this rejection be withdrawn.

VI. Claim Rejecti n Under 35 U.S.C. § 112, ¶ 2

Claim 10 has been rejected under 35 U.S.C. § 112, ¶ 2, for allegedly failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. Office Action at 5. The claim is allegedly indefinite for more than one reason. "First, no one particular disorder is recited. Second, the claim language may read on diseases not yet fully understood to be affected by dopamine receptor antagonists." *Id.* Applicants respectfully disagree with this rejection.

Without acquiescing to the allegation that the claim was indefinite, Applicants have amended claim 10 to recite the CNS disorders described in the specification on page 3, lines 29-33. This amendment obviates the two reasons given in support of the rejection. First, the claim now recites particular disorders. Second, the scope of diseases to be treated by the claimed methods is clearly delineated by those conditions listed in claim 10. Moreover, claim 10 amply meets the standard for claim definiteness.

Two separate requirements arise from the language of 35 U.S.C. § 112, ¶ 2: "(A) the claims must set forth the subject matter that applicants regard as their invention; and (B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant." M.P.E.P. § 2171. The claim meets the first requirement by describing a subset of the subject matter Applicants regard as their invention. The claim also meets the second requirement, by delineating the disease targets for the claimed methods of treatment. While the claim recites methods for treating broad classes of diseases, "[b]readth of a claim is not to be equated with indefiniteness." M.P.E.P. § 2173.04 (citing *In re Miller,* 441 F.2d 689, 169 U.S.P.Q. 597 (C.C.P.A. 1971)).

Applicants respectfully request that this rejection be withdrawn.

VII. Claim Rejection Under 35 U.S.C. § 103

Claims 1-11 have been rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Kruse et al. (EP 0190472). Office Action at 5. Allegedly, Kruse et al. "teaches a generic group of compounds which embraces applicant's instantly claimed compounds." *Id.* This is alleged even though it is admitted that "[t]he compounds made in [Kruse et al.] had a benzofuran core which differs from the benzoxazole core of the instant claims." *Id.* Applicants point out that formula (I) is not limited to a benzoxazole core, and respectfully disagree with this rejection.

Applicants do not acquiesce to the suggestion that a prima facie case of obviousness has been made. *See* M.P.E.P. § 2143. Nonetheless, because the evidence of unexpected results is so compelling, Applicants contend that if a prima facie case were made based on the disclosure of Kruse et al., that case would be strongly rebutted by the unexpected results reported in the specification. Applicants, some of whom co-authored Kruse et al., acknowledge that "it is known from EP 0190472 [Kruse et al.] that benzofuran- and benzodioxole-piperazine derivatives substituted at the other nitrogen atom of the piperazine group, have also psychotropic activity." Specification at 1, ll. 11-13. However, the present invention involves compounds that have potencies that surpass those of the compounds exemplified in Kruse et al. "The activity of the compounds [of the present invention] in this model was in the low microgram/kg range, which is surprisingly more active (by a factor 100 to 3000) compared to the compounds previously described in EP 0190472 [Kruse et al.][.]" Specification at 3, ll. 2-5.

Applicants urge the Examiner to consider the factors set forth in M.P.E.P. § 2144.08 when re-evaluating this rejection. Those factors include "differences between the closest disclosed prior art species . . . and the claimed subgenus or species," "the size of the prior art genus," "teachings of structural similarity," and "rebuttal evidence." M.P.E.P. § 2144.08(II).

For example, the Examiner has acknowledged that Kruse et al. discloses structurally different species. Office Action at 5. "When making an obviousness determination, Office personnel should consider the number of variables which must be selected or modified, and the nature and significance of the differences between the prior art and the claimed invention." M.P.E.P. § 2144.08(II)(A)(4)(c)(citation omitted).

Further, Kruse's disclosed genus is quite large considering, for example, that Kruse's A ring can be a 5-7 membered ring having a variable number of heteroatoms and substituents. Kruse et al. at 1, ll. 15-23. Regarding teachings of structural similarity, the M.P.E.P. guides: "consider any teaching or suggestion in the reference of a preferred species or subgenus that is significantly different in structure from the claimed species or genus. Such a teaching may weigh against selecting the claimed species or subgenus and thus against a determination of obviousness." M.P.E.P. § 2144.08(II)(A)(4)(c)(citation omitted).

For these reasons, Applicants respectfully request that the obviousness rejection over Kruse et al. be withdrawn.

CONCLUSION

Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this Amendment and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 7, 2004

By: _____
Jeremy M. Stipkala
Reg. No. 44,359

Attachments:

Abstract
R. Feenstra et al., SLV308, 26(2) Drugs of the Future 128 (2001)

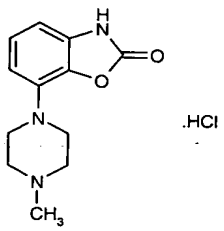
Drugs of the Future 2001, 26(2): 128-132

CCC: 0377-8282/2001

SLV308

Antiparkinsonian
Antidepressant
Anxiolytic
Dopamine D_2 Partial Agonist
5-HT_{1A} Agonist

7-(4-Methyl-1-piperazinyl)benzoxazol-2(3*H*)-one monohydrochloride



$C_{12}H_{15}N_3O_2.HCl$ Mol wt: 269.7304

CAS: 269718-83-4
CAS: 269718-84-5 (as free base)

EN: 290288

Synth sis

The synthesis of SLV308 was obtained as follows: The first step is the reduction of just one nitro group, which was accomplished by treating 2,6-dinitrophenol (I) with sodium sulfide in the presence of sodium hydrogencarbonate dissolved in a water/MeOH mixture to yield 2-amino-6-nitrophenol (II) in 62%. To construct the heterocyclic ring, (II) was reacted with carbonyldiimidazole in dry tetrahydrofuran to give the nitro benzoxazolinone (III) almost quantitatively. The reduction of the nitro group of (III) was performed in acetone/Raney-Ni, resulting in the corresponding aniline (IV) (72%). Transforming the aniline (IV) into the piperazine was done by heating (IV) and bis(2-chloroethyl)amine (V) in chlorobenzene at reflux temperature; after 70 hours the desired piperazine (VI) was obtained after chromatographic purification in 60% yield. The last step, introduction of the methyl group, was achieved by a reductive amination; formaldehyde, sodium triacetoxyborohydride and triethylamine dissolved in dichloroethane were added to (VI). After work-up, chromatographic purification and subsequent treatment with ethanolic HCl, SLV308 was isolated in 81% yield (1). Scheme 1.

Description

White solid, m.p. 302-3 °C.

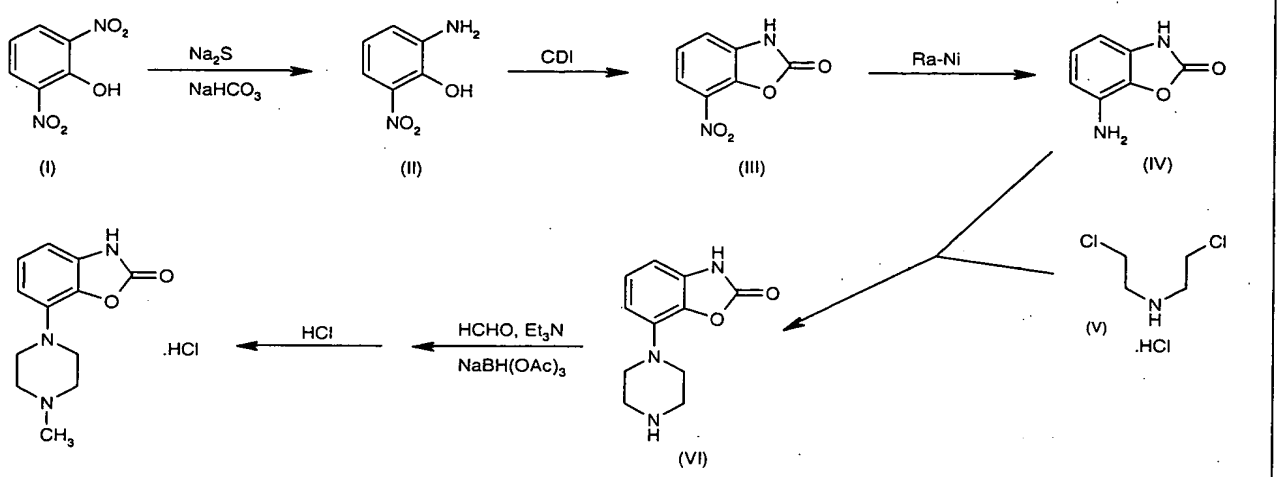
Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, primarily affecting dopaminergic neurons arising from the substantia nigra which project into the caudate nucleus and putamen. This system is critical in controlling motor patterns, and neurodegeneration in this pathway results in primary symptoms such as postural rigidity, bradykinesia and resting tremor. Moreover, many Parkinsonian patients also suffer from secondary symptoms like depression, sleep disturbances and dementia which can become more disabling than the primary ones.

Current therapy for Parkinson's disease focuses on alleviating the motor symptoms. Use of L-dopa as the precursor for dopamine synthesis has been shown to be effective in improving the motor functioning of patients. By using L-dopa, the rate-limiting step for the synthesis of dopamine, tyrosine hydroxylase, is by-passed, especially in combination with peripherally acting decarboxylase inhibitors. However, the effects of L-dopa treatment decline over the years and patients may experience characteristic situations in their performance, known as "on-off" effect. During the off-state, patients suffer weakness, akinesia and "freezing". In addition, patients may suffer

R. Feenstra, E. Ronken, T. Koopman, M. de Vries, A. McCreary, M. Stoker, K. van Charldorp, S. Long, G. van Scharrenburg*. Solvay Pharmaceuticals, P.O. Box 900, 1380 DA Weesp, The Netherlands. *Correspondence.

Scheme 1: Synthesis of SLV308



from "end of dose" deterioration in which the benefit of each dose becomes progressively shorter. For these reasons, the opinion to delay L-dopa treatment as long as possible has become more widely accepted.

Trying to substitute L-dopa treatment by dopamine agonists has led to the identification of the ergot compounds bromocriptine and pergolide as effective in PD. More recently, nonergot compounds such as ropinirole and pramipexole have been introduced and found equally effective in treating the symptoms (4,5) but with less side effects. These compounds all share the property of being full dopamine D_2 receptor agonists, when assayed for cAMP accumulation or GTPγS binding.

In the search for new therapeutic approaches for PD, it was considered that by using partial D_2 agonists, efficacious pharmacotherapy could be significantly prolonged while the incidence of side effects such as nausea, vomiting and hallucinations would be avoided or substantially decreased. In parkinsonian patients, with supersensitive postsynaptic dopamine receptors, full receptor agonists may rapidly desensitize the receptors. However, partial receptor agonists, such as SLV308, are less likely to induce this undesirable effect. In addition, partial receptor agonists are likely to induce a more consistent degree of postsynaptic receptor activation. Under conditions where synaptic levels of endogenous dopamine are low, SLV308 would act to supplement postsynaptic dopamine receptor stimulation. However, under conditions where high levels of endogenous dopamine are present, a partial agonist will antagonize the maximal effect of the endogenous agonist, thereby preventing overstimulation of the receptors. These pharmacological actions of SLV308 give the opportunity to create a situation in which the tone at postsynaptic dopamine receptors can be finely tuned in a sustainable manner.

When screened *in vitro*, compounds were selected that yielded partial agonism; subsequently, they were tested for their antiparkinsonian and potential antidepressant activity *in vivo*. Using this profile, SLV308 was selected as a compound showing extremely potent partial dopamine D_2 receptor agonism in combination with weaker full 5-HT_{1A} agonism, ultimately providing an antiparkinsonian as well as antidepressant and anxiolytic profile.

Pharmacological Actions

In order to assess dopamine D_2 receptor affinity, receptor binding was done using competition assays at rat striatal membrane preparations using [^{3}H]-spiperone as the radioligand (2). SLV308 was found to compete with radiolabeled spiperone with a pK_i of 7.5. A more complete receptor binding profile is shown in Table I.

To assess agonist efficacy and potency of compounds at dopamine D_2 receptors, we used cloned human D_2 receptors, stably transfected into CHO cells. Accumulation of radioactive cAMP from radiolabeled ATP (3) was induced by incubation with forskolin and in the presence of the phosphodiesterase inhibitor IBMX. D_2 receptor agonists can concentration-dependently attenuate cAMP accumulation. SLV308 was found to be a partial agonist with a pEC_{50} value of 7.5 and an efficacy of 0.55 (Fig. 1). Moreover, SLV308 was able to concentration-dependently antagonize the agonist actions of quinpirole with a pA_2 of 8.4, to about 50% with respect to control values. Therefore, it is expected that SLV308 will interactively control DA neurotransmission, *i.e.*, at low ambient DA concentrations, SLV308 will mimic DA effects by itself, whereas at high ambient DA concentrations, SLV308 is likely to exert antagonist properties, suppressing the maximal effect induced by endogenous DA. SLV308 also

Table I: Receptor binding profile of SLV308 (pK_i) for various receptors.

Receptor	pK_i value	Radioligand	Material
D_1	7.5	[^{3}H]-Dopamine	Rat striatum
D_2	7.5	[^{3}H]-Spiperone	Rat striatum
D_4	7.6	[^{3}H]-Spiperone	Human D4.2-CHO
5-HT_{1A}	7.5	[^{3}H]-8-OH-DAPT	Rat frontal cortex
5-HT_7	7.1	[^{3}H]-5-CT	Rat 5-HT_7-CHO
α_{1a}	7.1	[^{3}H]-Prazosine	Rat liver
α_{1b}	7.1	[^{3}H]-Prazosine	Rat liver
Others	< 6.0	Miscellaneous	

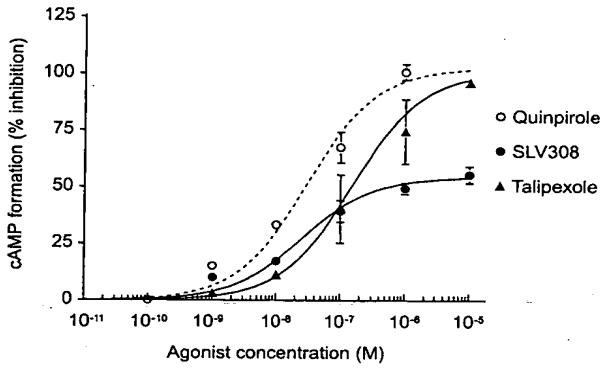


Fig. 1: Interaction of SLV308, quinpirole and talipexole with CHO cells, stably transfected by human dopamine D_2 receptors, as measured by cAMP accumulation. Agonist activity can be measured by the concentration-dependent attenuation of cAMP accumulation. D_2 receptor activation inhibits the accumulation of cAMP stimulated by forskolin (10^{-7} M). Quinpirole and talipexole completely attenuated cAMP formation, whereas SLV308 acts as a partial agonist.

weakly antagonized the effects of the full dopamine D_1 receptor agonist SKF-38393 with a pA_2 of 6.1.

Furthermore, SLV308 was found to be a weak but full 5-HT_{1A} receptor agonist with a pEC_{50} of 6.3. *In vivo*, SLV308 was found to possess α_1-adrenoreceptor agonistic activity.

The activity of SLV308 was further investigated by assessing its activity at presynaptic dopamine D_2 receptors. Striatal slices were prelabeled with [^{3}H]-dopamine and subsequently used in superfusion experiments. Release was stimulated by increased K^+ concentrations in the absence or presence of SLV308. SLV308 did not yield agonist activity in this preparation, but was found to completely and potently antagonize the agonist quinpirole with a pA_2 of 8.5. Apparently, SLV308 does not have enough intrinsic activity to exert agonist activity at presynaptic D_2 receptors.

Using microdialysis in rat nucleus accumbens, SLV308 lowered extracellular DA content with a lowest effective dose (LED) of 0.3 mg/kg p.o. and an ED_{75} of 0.4 mg/kg p.o., whereas on extracellular 5-HT no significant effects were observed at these doses. SLV308 was tested for its activity on locomotor behavior in open field tests. SLV308 lowered spontaneous activity with ED_{50} values of 0.02 mg/kg i.p. and 0.03 mg/kg p.o. However, in rats that were lesioned unilaterally by 6-OH-dopamine and checked for turning behavior using apomorphine, SLV308 produced contralateral turning behavior with an LED of 0.03 mg/kg p.o. In MPTP-treated common marmosets SLV308 at doses of 0.1 mg i.p. and above produced marked and long-lasting antiparkinsonian effects. These results indicate that SLV308 acts as a potent agonist in animal models of Parkinson's disease.

The putative antidepressant properties of SLV308 were assessed in the forced swim test and the differential reinforcement of low rates of responding (DRL-72). In the forced swim test SLV308 exerted potent antidepressant activity as measured by decreasing the immobility time by at least 8 sec. The observed ED_{50} was 0.2 mg/kg i.p. in Wistar rats and was 0.03 mg/kg i.p. in Hooded Lister rats. The antidepressant properties of SLV308 are probably mediated by D_2 receptors and 5-HT_{1A} receptors, as both 5-HT_{1A} receptor agonists such as 8-OH-DPAT and flesinoxan and D_2 receptor agonists like quinpirole and talipexole are active in the forced swim test.

In the DRL-72 paradigm, SLV308 showed an antidepressant profile with an LED of 0.87 mg/kg i.p. These effects are shared with both dopamine agonists and antagonists, as well as with 5-HT_{1A} receptor agonists and α_2 receptor agonists. Together, these data suggest antidepressant activity of SLV308.

SLV308 was also tested in behavioral paradigms, predictive for anxiolytic efficacy. Thus, in recording stress-induced ultrasonic pup vocalizations, SLV308 dose-dependently attenuated the number of calls with an LED_{50} of 0.1 mg/kg i.p. However, in the adult stress-induced ultrasonic vocalization paradigm, SLV308 attenuated the number of shock-induced ultrasonic calls with an ED_{50} of 0.006 mg/kg p.o. Moreover, when used for duration of action, SLV308 was still found to be effective 4 h after administration, with an ED_{50} of 0.09 mg/kg p.o.

In conclusion, the pharmacological profile of the non-ergot partial D_2 agonist SLV308 suggests that both motor and mood disturbances associated with Parkinson's disease can be treated.

Pharmacokinetics and Metabolism

The absorption of SLV308 in rats and cynomolgus monkeys was rapid and complete. The bioavailability was 60-80%. The $t_{1/2}$ was 2-8 h in rats and 5-12 h in monkeys. Several metabolic routes exist. To date, no pharmacologically active metabolites were found. *In vitro* metabolism by human microsomes was mediated primarily by CYP 1A2. No inhibitory effects on CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4 were observed. Excretion was mainly in urine. At high doses such as 6.5 mg/kg deviations from linear kinetics were observed. In the low and middle dose range kinetics were linear and not

sex-specific. SLV308 is considered to be an intermediate clearance drug.

Toxicology

To date, acute and chronic toxicology studies have been conducted in rats, mice, dogs and cynomolgus monkeys with the focus on rats and monkeys, being the species that mimic human metabolism of SLV308.

At low doses (about 0.2 mg/kg in rats and 0.07 mg/kg in monkeys; systemic exposure of about 30 ng·h/ml in rats to 100 ng·h/ml in monkeys) mild, CNS-mediated clinical signs were observed. At higher doses the same clinical signs were more pronounced.

Also observed (in rats but not monkeys) at the lower dose levels were a mild disturbance of water and electrolyte balance (indicated by increased water consumption and urine production) and slight changes in clinical chemistry parameters. Vomiting was a prominent effect in dogs and occurred occasionally in monkeys. In addition, at high doses (6.5 mg/kg) in rats body weight, liver weight and thymus weight were slightly reduced. At high doses (0.6 mg/kg) in monkeys, tremors were occasionally observed, water consumption (in females only) was increased and liver weight was increased or decreased, probably representing effects on glycogen storage. In rats, SLV308 caused transient increase in corticosterone levels (but not in prolactin or growth hormone levels); some of the effects on water/electrolyte balance and blood chemistry are consistent with increased glucocorticoid levels or other effects on the hypothalamic-pituitary-adrenal axis. Even at high exposures (about 750 ng·h/ml) there were no adverse, treatment-related effects in the 3-month study in monkeys upon body weight, food consumption, ophthalmology, electrocardioraphy, blood pressure, pulse rate, hematology, clinical chemistry, urinalysis, 24-h urine volume or macroscopic or microscopic pathology. At high doses (6.5 mg/kg) in the 6-month rat study there were also no adverse macroscopic or histopathologic abnormalities observed in any tissue. In this latter study in rats, all observed adverse responses and clinical signs were reversed and returned to normal after a 1-month recovery period.

The therapeutic index for SLV308 is considered large: in rats, the most sensitive species, a dose of about 1 mg/kg, corresponding to an exposure of 190-310 ng·h/ml, appeared to be the lowest dose that caused mild, reversible adverse effects while doses as low as 0.01 mg/kg were pharmacologically active.

SLV308 was tested in genotoxicity assays and there was no evidence to indicate a genotoxic risk to humans.

Clinical Studies

The safety and tolerability of SLV308 were assessed in a total of 51 healthy male subjects. Twenty seven subjects received one or more single doses ranging from 0.01-0.5 mg. In a multiple-dose study, 18 subjects received doses of up to 0.7 mg b.i.d. This dose was achieved after gradual titration over a period of 14 days, starting with a dose of 0.1 mg b.i.d. In a second multiple-dose study, 6 subjects received doses up to 1 mg t.i.d.

In the single-dose study, clear drug-related adverse events were observed with doses of 0.2 mg and higher. The tolerability after single administration of 0.5 mg was poor. The following adverse events were reported in decreasing order of frequency: nausea, general malaise, dizziness, asthenia, syncope, headache, vomiting, abdominal pain, somnolence and flu syndrome. Dose-related orthostatic hypotension was observed, especially in systolic blood pressure, which was accompanied by dizziness, nausea and general malaise.

The multiple-dose studies show that SLV308 is well tolerated up to doses of 1 mg t.i.d. Adverse events were reported with doses of 0.7 mg t.i.d. and higher. Compared to the single-dose study, the tolerability of SLV308 in this study was better. It can be concluded that tolerance to adverse events developed after slow upward titration.

The effects of SLV308 on hormones and body temperature in these studies suggest that, in the investigated dose range, the compound acts as an agonist at 5-HT_{1A} and D_2 receptors. In the single-dose study a dose-related increase in cortisol and hGH levels was observed with doses of 0.2 mg and higher. Decreases in prolactin levels were seen with doses of 0.01 mg and higher.

A slight decrease in body temperature was observed after administration of 0.4 mg (under fasting conditions) and 0.5 mg. Cognitive performance tests showed a slight trend for a dose related effect on the execution of the tests. In the multiple-dose studies decreases of prolactin levels were observed after all investigated doses, but evels were normalized within 12 h postdosing.

SLV308 was rapidly absorbed. Peak concentrations were reached within 0.5-4 h postdose. The mean half-life was around 1-3 h. The AUC and C_{max} data suggest linear kinetics in the dose range up to 1.0 mg t.i.d.

The excretion of unchanged SLV308 in urine is low (around 1%). Four subjects were genotyped as poor metabolizers for CYP2D6. These subjects had plasma levels in the same range as the extensive metabolizers.

Both the preclinical and clinical data suggest that SLV308 will be of value in treating parkinsonian patients. This is presently under examination.

Manufacturer

Solvay Pharmaceuticals, Inc. (NL).

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